Gender-related differences in hypertrophic cardiomyopathy: 30 years of experience in an Italian center

Sergio Bongioanni, Catia De Rosa, Martina Cortese, Barbara Mabritto, Alfredo Pizzuti, Stefania Luceri, Tommaso Forni, Massimo Pasquino, Maria Rosa Conte

Mauriziano Hospital, Turin, Italy. Received 12 October 2016; accepted 26 January 2017.

Summary. Introduction. Hypertrophic cardiomyopathy (HCM) is a genetic disease with a broad spectrum of clinical features and outcomes. The aim of our study was to assess gender-related differences in patients with HCM and their possible influence on management and outcome. Methods. We retrospectively studied data from patients followed at our referral center for HCM in Turin, from 1983 to 2015. Results. Of 573 patients enrolled, 352 (61%) were men and 221 (39%) women. At first evaluation, women were older and more symptomatic than men (57 ± 19 years vs 50 ± 10 years, p < 0.001; NYHA class 1.59 ± 0.66 vs 1.36 ± 0.55, p < 0.001) and more frequently presented the obstructive form (47% vs 39%, p = 0.045). During follow-up, a cardiac magnetic resonance study and a treadmill test were performed more frequently in men [175 (57%) vs 82 (43%), p = 0.002; 237 (78%) vs 106 (56%), p < 0.001]. Pharmacological and invasive treatment did not differ between sexes. Mortality was higher in women than in men (17% vs 10%, p = 0.037). The main cause of HCM-related death were heart failure in females and sudden cardiac death in males. A NYHA class >1, atrial fibrillation and the obstructive form at first evaluation were all predictors of HCM-related mortality, while gender was not. Discussion. In HCM, an autosomal dominant disease, prevalence is higher in men. Women are older and more symptomatic and have higher HCM-related mortality. Many factors, such as a different phenotypical expression, the influence of hormonal status on myocardial hypertrophy and greater attention to cardiovascular diseases in males may play a role. Being aware of these differences is important to reduce any sex referral bias.

Key words: hypertrophic cardiomyopathy, gender difference.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic disease affecting the heart, with an estimated prevalence in the overall population of 0.2%. The disease is caused by mutations in genes encoding sarcomeric proteins and is inherited with an autosomal dominant pattern, with a 50% probability of transmission from parents to offspring, whether male or female. Some gender differences have been described not only in disease prevalence which is greater in men than in women, but also in clinical presentation and age at diagnosis. The causes are not completely understood and may involve a possible multifactorial etiology.
Objective

Aims of our study are to identify the presence of gender-related differences in a population affected by HCM from a referral center in Turin and to understand if such differences could influence therapeutic strategies and outcome.

Materials and methods

We retrospectively collected and analyzed clinical history, clinical and instrumental data of consecutive patients with documented HCM evaluated at Mauriziano Hospital (Turin, IT), between 1983 and 2015.

Diagnosis of HCM was based on the evidence of an interventricular septum thickness ≥15 mm detected by 2D echocardiography, or ≥13 mm in patients with a family history of HCM, in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy identified. In children, a thickness ≥+2 standard deviation (SD) was considered to have diagnostic value. A definite diagnosis of HCM was made during the first evaluation at our center.

An obstructive form of HCM was defined in presence of left ventricle outflow tract obstruction with maximum gradient ≥30 mmHg.

Risk for sudden cardiac death (SCD) was assessed both with known risk factors [non-sustained ventricular tachycardia (NSVT) on 24-hour Holter monitoring, massive hypertrophy (maximum wall thickness >30 mm), recent unexplained syncopal episodes, abnormal blood pressure response (ABPR) during treadmill test and family history of SCD] and with HCM Risk-SCD calculator.

Patients underwent regular clinical and instrumental follow-up. Since 2006 a complete cardiac magnetic resonance (CMR) study with late gadolinium enhancement (LGE) was offered to all patients.

Patients who only attended the first evaluation were considered lost to follow-up.

SCD was defined as an unexpected collapse due to HCM occurring within 1 hour from the onset of symptoms in patients previously experiencing a relatively stable clinical course. Heart failure (HF)-related death was established in patients who experienced a progressive deterioration of cardiac function resulting in end-stage HCM (ejection fraction <50%). Stroke-related death was considered when a patient died as a result of ischemic stroke.

Statistical methods

Data are expressed as mean ± SD or median [interquartile range] for quantitative variables, absolute frequency and percentage for qualitative variables. Student’s t-test for independent data, ANOVA test and non-parametric tests were used based on the distribution of continuous variables; chi-square for non-continuous variables.

Relative risks and 95% confidence intervals were calculated using univariate and multivariate Cox proportional-hazards regression. Survival analysis was performed by Kaplan Meier estimates and Log Rank Test for establishing differences among groups.

The p-values are two-sided and considered significant when <0.05. Data were analyzed by statistical software SPSS 20.0 (Chicago, Illinois).

Results

First evaluation

A total of 573 patients were enrolled, of whom 352 (61%) were men (Table 1). Mean age at diagnosis was 53 ± 18 years. Women were diagnosed 7 years later on average (p <0.001). Breaking down the population by age group, male patients were more frequently diagnosed under the age of 60 years, while females were diagnosed more often after the age of 60 years (p <0.001).

Females were in a higher NYHA functional class than males (1.59 vs 1.36, p <0.001): there were 237 men (67%) and 109 women (49%) in NYHA FC I (p <0.001).

We found no difference in family history of HCM between the two groups at diagnosis (p = 0.415).

Echocardiographic parameters. An obstructive form of the disease was found in 239 patients (42%), with a higher prevalence among women (47% vs 39%, p = 0.045). Among obstructive patients, basal gradient did not differ between sexes, while gradient elicited by provocative maneuvers was higher in women (68 vs 47 mmHg p = 0.015). Maximum wall thickness was 19.21 ± 4.45 mm, with no gender-related difference (p = 0.168).

Ejection fraction % (EF%) was 64 ± 8 (p = NS). End-stage HCM (EF <50%) was found in 19 (3%) patients and was equally distributed between sexes (p = 0.810).

The frequency of risk markers for SCD was similar in males and females (Table 1).

Mean 5-years SCD risk estimated with HCM Risk-SCD calculator at first evaluation was 2.6%. Twenty-three patients (4%) had an elevated arrhythmic risk (>6%) while the vast majority (83%) were at low risk (<4%). Mean SCD risk was higher in men (2.72 vs 2.40, p = 0.049). We found no difference in atrial fibrillation (AF) prevalence and patterns.

At first evaluation, women were more frequently on drug therapy than men (77% vs 67%, p = 0.01).
<table>
<thead>
<tr>
<th>Table 1. Baseline clinical and echocardiographic features of 573 patients according to gender.</th>
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<tbody>
<tr>
<td><strong>Overall</strong></td>
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<tr>
<td>No. of patients</td>
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<tr>
<td>Age at diagnosis, yrs</td>
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<tr>
<td>Age at diagnosis, yrs</td>
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<tr>
<td>≤ 20</td>
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<td>21-40</td>
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<tr>
<td>41-60</td>
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<tr>
<td>&gt; 60</td>
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<tr>
<td>Family history of HCM</td>
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<tr>
<td>NYHA FC</td>
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<td>I</td>
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<tr>
<td>II</td>
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<td>III</td>
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<td>IV</td>
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<tr>
<td>Mean NYHA FC</td>
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<td>Echocardiographic measurements</td>
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<td>Obstructive HCM</td>
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<td>Max LV outflow gradient, basal [median – IQR]</td>
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<td>Max LV gradient with Valsalva [median – IQR]</td>
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<tr>
<td>Mitral regurgitation</td>
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<tr>
<td>Mild</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Severe</td>
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<tr>
<td>Max LV thickness, mm</td>
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<td>≤15</td>
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<tr>
<td>16-19</td>
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<td>20-24</td>
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<td>25-29</td>
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<tr>
<td>≥ 30</td>
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<tr>
<td>Max LV thickness, mm</td>
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<tr>
<td>Left atrium diameter, mm</td>
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<tr>
<td>Ejection fraction, %</td>
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<tr>
<td>Ejection fraction % ≤ 50%</td>
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<tr>
<td>LVEDD</td>
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<td>Atrial fibrillation</td>
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<tr>
<td>Paroxysmal</td>
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<td>Chronic</td>
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<tr>
<td>Family history of SCD</td>
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<td>Syncope</td>
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<td>On medical treatment</td>
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<td>Beta-blockers</td>
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<td>Calcium-antagonists</td>
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<td>Amiodarone</td>
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<td>Oral anticoagulants</td>
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<td>ESC RISK mean</td>
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<tr>
<td>ESC risk</td>
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<td>&lt;4%</td>
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<tr>
<td>4 - 6%</td>
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<tr>
<td>&gt; 6%</td>
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</tbody>
</table>

HCM: hypertrophic cardiomyopathy; NYHA FC: New York Heart Association functional class; SAM: systolic anterior motion; EF: ejection fraction; SCD: sudden cardiac death; LV: left ventricle; LVEDD: left ventricular end diastolic diameter; ESC: European Society of Cardiology.
Follow-up
In all, 494 patients continued the follow-up, with a similar proportion of males and females (M 62% vs F 38%, p = NS). Seventy-nine patients (14%) were lost during follow-up (Table 2). Mean follow-up time was 87 ± 72 months (7 years). At last clinical evaluation women were older (63 vs 57 years; p <0.0001) and in a higher NYHA FC (1.85 vs 1.52, p <0.001). Most of the male patients (167, 55%) remained asymptomatic (NYHA FC I), while most of the females (216, 44%) were slightly limited (NYHA FC II). Considering advanced NYHA classes, more than two thirds of patients were women.

Echocardiographic parameters. Also at follow-up, the obstructive form was more frequent among women (42% vs 32%, p = 0.019). Among obstructive patients, basal and maximal gradient were similar in both sexes and were reduced compared to first evaluation (Table 2).

A CMR study was performed in 257 (52%) patients, of whom 175 (57%) were males and 82 (43%) females (p = 0.002). LGE was detected in 145 (56%) patients, with no gender-related differences (p = 0.662).

A treadmill test was performed in 343 (69%) patients, significantly more often in male patients (78% vs 56%; p <0.001). We found no significant differences in ABPR and arrhythmias (p = 0.580).

A total of 433 patients (88%) were on drugs: 360 (73%) on beta blockers, with no gender difference (p = NS). Women were more often on calcium antagonists (18% vs 11%, p = 0.024) while there was no difference in the use of amiodarone and warfarin. Surgical myectomy was performed in 29 patients (6%) and implantable cardiac defibrillator (ICD) was implanted in 38 patients (8%), without gender differences (Table 2).

Prognosis
During follow-up, 63 patients died (13%) (Table 2). A higher mortality among women (17% vs 10%, p = 0.037) was observed. HCM-related deaths were 52 (82% of all deaths). Mean age at death was 61 ± 17 years with an increasing trend towards older age in women (65 vs 57 years, p = 0.074).

Causes of death were congestive HF (48%), SCD (25%), cerebrovascular (9%) and extracardiac causes (17%). The main causes of death were HF in females (62%), while in males were either congestive HF (32%) or SCD (42%), with a significant gender difference (p = 0.023) (Table 2).

Patients in NYHA FC >1 (p <0.001), AF (p <0.0001) and/or with the obstructive form of the disease (p = 0.008) at first evaluation, had worse survival (Figure 1-2-3). At multivariate analysis, NYHA FC >1 (p <0.005, RR 2.67), atrial fibrillation (p = 0.017, RR 2.08) and obstructive HCM (p = 0.03, RR 1.83) were all predictors of HCM-related mortality in our population, while gender was not (Table 3).

Discussion
In our population, we observed a greater prevalence of HCM in male gender, as already described in other studies. Since HCM is a genetic disease transmitted with an autosomal dominant pattern of inheritance, a different prevalence between the two sexes is unexpected. However, the vast majority of our patients did not undergo genetic testing and we cannot therefore exclude that some patients diagnosed as HCM could actually have different forms of left ventricle hypertrophy.

Moreover, females genotypically affected could not come to a complete phenotypical expression (incomplete penetrance) and therefore remain undiagnosed. While most of the male patients are diagnosed during adolescence and early adulthood, women are often diagnosed later, after the age of 60 years. Explanations might be attributed to different factors, such as a generally lower degree of attention to cardiovascular risk and lower participation in screening programs among women. Furthermore, in young people, HCM is at times suspected based on electrocardiographic abnormalities found during medical examination for military service or agonistic activity and is generally more common among young males.
<table>
<thead>
<tr>
<th>Table 2. Clinical and echocardiographic features at follow-up.</th>
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<tr>
<td><strong>Overall</strong></td>
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<tr>
<td>No. patients</td>
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<td>No. patients lost to FU</td>
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<tr>
<td>Age at final evaluation, yrs</td>
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<td>Follow up, months</td>
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<tr>
<td>Final NYHA FC</td>
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<td>I</td>
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<td>II</td>
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<td>Oral anticoagulant</td>
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<tr>
<td>Syncope in FU</td>
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<tr>
<td>Surgical septum myectomy</td>
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<td>Alcohol septal ablation</td>
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<td>ICD</td>
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<td>Pacemaker</td>
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<td>Treadmill test</td>
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<td>Response to treadmill test</td>
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<tr>
<td>Normal</td>
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<td>Hypotensive</td>
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<td>Arrhythmic</td>
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<td>Ischemic</td>
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<td>CMRI</td>
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<td>LGE</td>
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<td>LGE present</td>
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<td>Echocardiographic measurements</td>
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<td>Obstructive HCM</td>
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<td>Left atrium, mm</td>
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<tr>
<td>Ejection fraction, %</td>
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<td>LVEDD, mm</td>
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<tr>
<td>Death</td>
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<tr>
<td>Age of death, years</td>
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<tr>
<td>Cause of death</td>
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</tbody>
</table>

- FU: follow up; SAM: systolic anterior motion; HCM: hypertrophic cardiomyopathy; ICD: implanted cardiac defibrillator; LV: left ventricle; LVEDD: left ventricular end diastolic diameter; CMRI: cardiac magnetic resonance imaging; LGE: late gadolinium enhancement.
We found no gender-related differences either in the number of invasive procedures aimed at reducing obstruction, such as surgical myectomy. Nevertheless, during follow-up, women continued to be more symptomatic.

The reason for the lower referral to CMR that we observed in women may be due to a younger age of males at diagnosis. In this phase, there is greater attention to a thorough disease characterization; furthermore, women have a lower degree of acceptance of this exam especially due to claustrophobia. Given that CMR is a very useful tool for HCM definition and management, we are well aware that all effort should be made to implement the referral of women to CMR studies.

Since some of the CMR studies were rather old, we were not able to evaluate the extent of LGE in the overall population. It was detected in more than 50% of patients without any gender difference. As far as we know so far, no differences in gender prevalence and distribution of LGE have been reported. Anyway, it should be stressed that the best scar quantification techniques are still a matter of debate.

We would like to stress that in women there is a trend towards higher HCM-related mortality. In our population, heart failure-related death is more common in women. There was a low number of SCDs, of them 13 among men, and this might suggest that SCD is more frequent among men, as previously reported.

**Figure 1.** Kaplan Meier survival curves stratified by NYHA functional class at first evaluation. NYHA FC: New York Heart Association functional class.

**Figure 2.** Kaplan Meier survival curves stratified by the presence of left ventricle outflow obstruction at diagnosis. HCM: hypertrophic cardiomyopathy

**Figure 3.** Kaplan Meier survival curves stratified by atrial fibrillation at diagnosis. AF: atrial fibrillation.
From our survival analysis, as in study on prognostic significance of left ventricle outflow obstruction in Autore et al. and Olivotto et al., independent predictors of HCM-related mortality at first evaluation were the severity of HF symptoms (NYHA FC >1), the obstructive form and atrial fibrillation. The first two characteristics were more frequent among women, while there was no gender difference in AF prevalence either at diagnosis or at follow-up. AF occurs in around 25% of patients and is a predisposing factor for higher risk of thromboembolic events and progression to heart failure, especially in younger patients. Oral anticoagulant therapy and pharmacological maintenance of sinus rhythm are fundamental in preventing adverse events, such as stroke and heart failure.

It is yet to be understood why women have a higher mortality notwithstanding a similar use of drugs and procedures known to impact on survival. Whether it is due to a higher prevalence of comorbidities (hypertension, diabetes, overweight etc.) or to differences in a peculiar phenotypical expression of the disease (dystolic dysfunction and microvascular defects) is still unknown. We believe this hypothesis is worth further investigation.

Conclusions

In our cohort of patients, women were underrepresented and older at diagnosis. Their condition was also more obstructive and symptomatic. Female HCM-related mortality was higher than in men and their first cause of death was HF. Reasons for these differences are largely unclear but a different phenotypical expression, the influence of hormonal status on myocardial hypertrophy and “social” factors may play a role.

### Table 3. Predictors of HCM-related death based on univariate and multivariate Cox proportional hazard regression model.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.52 (0.91 – 2.52)</td>
<td>0.12</td>
</tr>
<tr>
<td>Obstructive form of HCM</td>
<td>1.973 (1.18 - 3.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>NYHA FC &gt; I</td>
<td>2.54 (1.62 – 3.93)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AF at first evaluation</td>
<td>2.97 (1.70 – 5.18)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Drugs at first evaluation</td>
<td>1.73 (0.96 – 3.12)</td>
<td>0.06</td>
</tr>
<tr>
<td>Family history of HCM</td>
<td>0.92 (0.55 – 1.55)</td>
<td>0.75</td>
</tr>
<tr>
<td>SCD history at first evaluation</td>
<td>0.62 (0.27 – 1.44)</td>
<td>0.24</td>
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<tr>
<td>Syncope at first evaluation</td>
<td>1.32 (0.57 – 3.10)</td>
<td>0.53</td>
</tr>
<tr>
<td>NSVT at first evaluation</td>
<td>1.06 (0.61 – 1.84)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

NI: not included in multivariate analysis; RR: relative risk based on Cox regression analysis; CI: confidence interval; HCM: hypertrophic cardiomyopathy; NYHA FC: New York Heart Association functional class; SCD: sudden cardiac death; NSVT: not sustained ventricular tachycardia.

### Key messages

- Hypertrophic cardiomyopathy (HCM) is a genetic disease with a broad spectrum of clinical features and outcomes.
- In our study, we assess gender-related differences in patients with HCM and their possible influence on disease outcome.
- HCM prevalence is greater in men.
- Women are older and more symptomatic and have a higher mortality than men.
- Mortality predictors are obstructive form of HCM, NYHA functional class >1 and atrial fibrillation at first evaluation.
References


Conflict of interest statement: the Authors declare no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Correspondence to
Martina Cortese
Corso Vittorio Emanuele II 165
10139 Turin (Italy)
email martin89@libero.it, martina.cortese@edu.unito.it
Tel (+39) 333 5493975